

***IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES***

APPELLANT: Muir
SERIAL NO.: 10/812,776 GROUP NO.: 1657
FILING DATE: March 29, 2004 EXAMINER: V. Afremova
TITLE: MATERIALS AND METHODS FOR NERVE GRAFTING,
SELECTION OF NERVE GRAFTS, AND IN VITRO NERVE TISSUE
CULTURE

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

REPLY BRIEF

Grounds of Rejection Addressed Herein

This reply brief is submitted pursuant to 37 C.F.R. §41.41 in reply to the Examiner's Answer of August 7, 2008 (the "Answer"). In particular, this brief addresses the following points raised or erroneously relied upon by the Examiner in the Answer:

- The Examiner has mischaracterized a key claim element that requires degrading chondroitin sulfate proteoglycan ("CSPG") of a nerve graft.
- La Fleur, Lassner, and Dennis each fail to teach or suggest, among other things, degrading CSPG of a nerve graft.
- The Examiner has mischaracterized and misunderstands Appellant's arguments regarding the rejection under 35 U.S.C. § 103(a).

For the reasons that follow, Appellant maintains that the Examiner's reasoning reflects a fundamental misunderstanding of the invention and the cited art.

Arguments

- I. The Examiner mischaracterizes a key claim element that requires degrading CSPG of a nerve graft.

In the Answer, the Examiner asserts that “[t]he limitations such as ‘degrading CSPG’ and ‘enhancing post-implantation’ are the intended effects of ‘*in vitro* culturing’ as claimed.”¹ In subsequent anticipation rejections, the Examiner alleges that insofar as the cited references describe a culturing step, they anticipate the claims. We respectfully submit that, under any reasonable reading, claims 1 and 38 clearly require degrading CSPG by *in vitro* culturing — not simply *in vitro* culturing in a generic sense, which might not produce the claimed effect.

Specifically, claims 1 and 38 recite “degrading, by *in vitro* culturing, chondroitin sulfate proteoglycan of a nerve graft,” which is amply supported throughout the specification. For example, degrading CSPG of a nerve graft can be achieved by application of CSPG-degrading enzyme and/or by *in vitro* culturing.² With regard to degrading CSPG by *in vitro* culturing, the specification explains:

The present invention also concerns methods of culturing nerve tissue for implantation into a human or animal. The culture methods of the subject invention involve “predegenerating” the nerve tissue *in vitro*, which, following engraftment, improves the ability of regenerating axons to traverse the interface between the graft and host nerve tissue. Without being bound by theory, the culturing methods of the subject invention allow the living nerve cells to express CSPG-degrading enzymes and promote Schwann cell proliferation, as would occur naturally *in vivo* during the remodeling process of nerve degeneration.³

The Examiner takes issue with the specification on several new grounds. First, the Examiner alleges that certain “definitions” in the specification at page 27, lines 10-23, which includes the excerpt above, are “rather broad.”⁴ Appellant respectfully submits that, whether or not any definitions in the specification are rather broad, the claimed step of degrading CSPG is clear and fully compliant with the requirements of §112. Specifically, the claimed step requires degrading, by *in vitro* culturing, CSPG of a nerve graft. As explained in the excerpt above, the culturing methods allow the living nerve cells to express CSPG-degrading enzyme. To the

¹ Answer at pgs. 3-4.

² Specification, pgs. 18-20 and 27-28, respectively.

³ Specification, pg. 27, lines 16-23.

⁴ Answer, pg. 10.

extent that the Examiner intended to allege that Appellant's *claim terms* are "rather broad," Appellant respectfully submits that breadth of a claim is not indefiniteness.⁵ The claims clearly recite degrading CSPG of a nerve graft by *in vitro* culturing, which is consistent with the specification. Thus, the claims are clear and definite.

In addition, the Examiner argues that "both applicant's arguments and definitions are circular and they do not clearly point out any specific parameters for the culture conditions during culturing step and/or they do not clearly point out any specific elements as encompassed in the step of 'degrading by *in vitro* culturing.'"⁶ Appellant respectfully submits that the teaching in the specification is not circular. In various sections — for example, the above-quoted passage, the description of the Examples section entitled "Nerve explant culture for predegenerating experiments,"⁷ the description of Example 11, entitled "The Neurite-Promoting Activity of Cultured Nerve Segments,"⁸ and the description of Example 18, entitled "Cultured Nerve as Acellular Interpositional Grafts"⁹ — Appellant describes culturing methods for degrading CSPG of a nerve graft. The disclosed methods activate CSPG-degrading enzymes endogenous to the nerve graft, and thereby enhance axonal regeneration into the nerve graft.

Appellant respectfully submits that the step of degrading, by *in vitro* culturing, CSPG of a nerve graft is clear, supported by, and consistent with Appellant's application and, therefore, the Examiner's indefiniteness rejection is improper. In particular, it is inappropriate to interpret the claims as simply reciting a culturing step, and nothing more, and it is inappropriate to apply such an interpretation against the references that the Examiner applies.

⁵ MPEP § 2173.04 ("Breadth of a claim is not to be equated with indefiniteness. *In re Miller*, 441 F.2d 689, 169 USPQ 597 (CCPA 1971). If the scope of the subject matter embraced by the claims is clear, and if applicants have not otherwise indicated that they intend the invention to be of a scope different from that defined in the claims, then the claims comply with 35 U.S.C. 112, second paragraph.")

⁶ Answer, pg. 10.

⁷ Specification, pg. 37, line 20 – pg. 38, line 10.

⁸ Specification, pg. 50, line 16 – pg. 51, line 4.

⁹ Specification, pg. 55, line 9 – pg. 56, line 23.

II. La Fleur, Lassner, and Dennis each fails to teach or suggest, among other things, degrading CSPG of a nerve graft.

A. La Fleur

In the Answer, the Examiner indicates that La Fleur's first organ culture protocol¹⁰ is no longer a basis for her rejection.¹¹ Instead, the Examiner asserts that La Fleur's second protocol teaches "the active steps of culturing nerve segments and killing cells in the nerve segment by chemical treatment."¹² As noted above, however, Appellant's claims 1 and 38 recite the step of degrading CSPG of a nerve graft by *in vitro* culturing, which La Fleur does not describe explicitly or inherently.

La Fleur's second protocol is not the same as Appellant's claimed degrading step. Rather, La Fleur's second protocol is designed "[t]o test the effect of growth factors and macrophage-conditioned medium on TIMP-1 expression" from segments of sciatic nerve.¹³ Unlike Appellant's step of degrading CSPG by *in vitro* culturing, which allows CSPG-degrading enzymes endogenous to the nerve graft to perform under physiological conditions, La Fleur adds exogenous macrophage-conditioned medium from lipopolysaccharide-stimulated mouse peritoneal exudate macrophages or various recombinant growth factors to elicit potential changes in TIMP-1 expression from the sciatic nerve segments.¹⁴ La Fleur indicates that these recombinant cytokines and the medium conditioned by activated macrophages (as described in La Fleur's second protocol) "induced TIMP-1 expression in nerve explants in culture."¹⁵ According to La Fleur, TIMP-1 protects basement membrane type IV collagen from degradation in cryostat sections of nerve *in vitro*.¹⁶ Accordingly, the recombinant cytokines and conditioned medium of La Fleur's second protocol preserve basement membrane by upregulating TIMP-1 *in vitro*, which is antithetical to the claimed requirement of degrading CSPG.

Moreover, LaFleur's focus on macrophage exudate in the second protocol is unrelated to Appellant's invention. For example, in Example 17, "Cell Distributions and Axonal

¹⁰ La Fleur, pg. 2312, col. 2, para. 1.

¹¹ Answer, pg. 12.

¹² *Id.*

¹³ La Fleur, pg. 2312, col. 2, para. 2.

¹⁴ *Id.*

¹⁵ La Fleur, pg. 2322, col. 1, para. 3.

¹⁶ La Fleur, abstract.

Degeneration in the Cultured Nerve Segments,” the specification states that “the nerve explants *in vitro* represent a model of nerve degeneration in which the contribution of Schwann cells may be assessed independently from those of invading macrophages” because macrophages “did not invade the inner nerve compartments during culture.”¹⁷

Further, in response to La Fleur’s description of treating the nerve tissue with TRIzol, an agent that can cause necrosis, coma, and death, the Examiner asserts that one of skill in the art would “rinse the tissue grafts before graft implantation.”¹⁸ However, TRIzol (phenol) covalently binds to tissue,¹⁹ so washing would be ineffective. Indeed, even apart from the effectiveness of washing, phenol has neurotoxic effects. As indicated by the Board in the decision of a companion case, “it is clear that the claim requires a ‘nerve graft for implantation’ which must be capable of being used in a nerve graft technique.”²⁰ Given the toxicity of phenol, it is at best highly uncertain that a viable graft would be obtained regardless of the (dubious) effectiveness of washing. One of skill in the art simply would not utilize La Fleur’s tissue for a nerve graft.

B. Lassner

Regarding Lassner, the Examiner argues that Appellant’s “rejected claims do not recite any specific conditions that lead to the intended effects such as promoting degradation of CSPG.”²¹ However, Appellant’s rejected claims 1 and 38 specifically recite the step of degrading, by *in vitro* culturing, CSPG of a nerve graft. As discussed in the Appeal Brief, the activities described in Lassner’s first series of experiments do not and cannot fulfill the requirements of Appellant’s claims. In Appellant’s method, if there is no physiological activity, there is no degradation of CSPG and, thus, no enhancement of post-implantation axonal traversal of an interface between the nerve graft and host nerve tissue.²²

¹⁷ Specification, pg. 54.

¹⁸ Answer, pg. 13.

¹⁹ See, e.g. IDS Reference C6, pg. 8.

²⁰ *Ex Parte* David F. Muir, BPAI Appeal No. 2008-3327, pgs. 6-7 (June 17, 2008) (routine opinion), available at http://des.uspto.gov/Foia/DispatchBPAIServlet?Objtype=ser&SearchId=10218315&SearchRng=docDt&txtInput_StartDate=&txtInput_EndDate=&docTextSearch=&page=60. Appellant notes that the present claims similarly recite “a nerve graft suitable for subsequent implantation.” See claims 1 and 38.

²¹ Answer, pg. 13.

²² Specification, page 56, lines 17-19.

The Examiner's Answer focuses on the second series of experiments in Lassner.²³ In these experiments, nerve grafts were prepared, dissected into small segments, placed in a culture dish containing Dulbecco's Modified Eagle Medium, and maintained at 5% CO₂/95% air for two days. The tissue segments were then evaluated morphologically, fixed with methanol at -18°C, and immunohistologically stained without any reimplantation. Thus, these experiments involve preparation of histological samples and do not describe degrading, by *in vitro* culturing, CSPG of a nerve graft. The described conditions not only fail to create a graft in accordance with the present claims; they fail to create *any graft at all* because histological samples (i.e., thin transverse sections of the nerve for microscopic evaluation) do not function as nerve grafts. Moreover, there is no indication that Lassner's samples comprise degraded CSPG or have an intact basal lamina tube structure.

Lassner also fixes the histological samples with methanol, a known neurotoxin and that can have irreversible effects.²⁴ The Examiner attempts to sidestep this deleterious treatment by arguing that, as with TRIzol, one of skill in the art would rinse the tissue grafts before graft implantation.²⁵ Beyond the fact that washing might simply be ineffective, the suggestion of treating a nerve graft for implantation with a neurotoxin defies logic. Indeed, it is widely recognized that "fixing" a tissue sample for histology will render it unacceptable for other tests, not to mention unacceptable for implantation. As noted above, the Board has indicated that "it is clear that the claim requires a 'nerve graft for implantation' which must be capable of being used in a nerve graft technique."²⁶ Appellant respectfully submits that Lassner's histological samples are not grafts, and certainly are not suitable for implantation, as required by Appellant's claims.

C. Dennis

Regarding Dennis, the Answer indicates that "the final effects with regard to remodeling nerve tissue segment *in vitro* are considered to be the same as result of the same active step of '*in*

²³ Lassner, pg. 148, col. 2 – pg. 149, col. 1.

²⁴ See, e.g. IDS Reference C8, sections 11 and 15.

²⁵ Answer, pg. 14.

²⁶ *Ex Parte* Muir, BPAI Appeal No. 2008-3327 at pgs. 6-7.

vitro culturing’.”²⁷ Again, Appellant’s claims 1 and 38 recite a step of degrading, by *in vitro* culturing, CSPG of a nerve graft, which Dennis does not teach or suggest, explicitly or inherently. Specifically, Dennis describes a method of acellularization and does not include a *degradation step by in vitro culturing*, as required by Appellant’s claims.

In her Answer, the Examiner dismisses the fact that Dennis’s use of sodium deoxycholate and TRITON-X 100 destroys the basal lamina tube structure, contending that “[t]his argument does not appear to have any persuasive grounds for the very least reason that the limitation ‘intact basal lamina tube structure’ is encompassed in the first step of ‘degrading by *in vitro* culturing’ of an intermediate product in the presently claimed method.”²⁸ The Examiner does not explain how a claim that requires an intact basal lamina tube structure can be anticipated by a reference in which the basal lamina tube structure is destroyed. Selective degradation of CSPG by *in vitro* culturing in a manner that maintains an intact basal lamina tube structure, as required by Appellant’s claims, is not and cannot be equated to acellurization and destruction of the basal lamina tube structure as described by Dennis. Indeed, the Sondell method’s use of sodium deoxycholate and TRITON-X 100, as repeated by Hudson and as cited by Dennis, “appears to fragment the basal laminae.”²⁹

Finally, the Answer contends that if Dennis’ tissue “is capable of performing the intended use [of Appellant’s claim], then it meets the claim.”³⁰ Whether or not this standard is even appropriate to a method claim, it is a standard that Dennis does not meet. For example, Appellant’s method requires enhanced post-implantation axonal traversal of an interface between the nerve graft and host nerve tissue. Although Dennis may describe nerve grafts that support axonal regeneration, it does not disclose degradation of CSPG or enhancement of post-implantation axonal traversal of an interface between the nerve graft and host nerve tissue. Nor can it be assumed that these requirements occur inherently. Appellant’s Example 18 and Figure 20A, for example, indicate that axonal regeneration into acellular nerve grafts is enhanced by *in vitro* predegeneration, but that axonal growth occurred within the basal lamina tubes in both the predegenerated and control (i.e., acellular but not predegenerated) conditions. Thus, the mere

²⁷ Answer, pg. 15.

²⁸ Answer, pg. 16.

²⁹ Hudson, page 1356, col. 2, first paragraph.

³⁰ *Id.*

existence of a graft supporting axonal regeneration is an insufficient basis to infer degradation of CSPG, enhancement of post-implantation axonal traversal, or structural equivalence to grafts produced in accordance with the present claims.

III. The Examiner mischaracterizes and misunderstands Appellant's arguments regarding the rejection under 35 U.S.C. § 103(a).

In the Answer, the Examiner misunderstands Appellant as arguing "that there is no suggestion to combine the cited references" of Dennis, La Fleur, Ide, and Evans.³¹ This same misunderstanding appears in the Office Action dated January 30, 2008, from which Appellant filed this appeal. In fact, Appellant's position, as stated throughout prosecution and in the Appeal Brief, is:

Both Dennis and La Fleur fail to describe *degrading, by in vitro culturing, CSPG of a nerve graft*. In addition, the methods of both Dennis and La Fleur result in grafts that are structurally different from grafts produced in accordance with the present claims, and also involve chemicals that simply are not compatible with a *method of preparing a nerve graft suitable subsequent implantation*. Ide and Evans fail to cure the deficiencies of Dennis and La Fleur, alone or in combination.³²

...

Accordingly, there is no reason why one of skill in the art would modify the teachings of Dennis and/or La Fleur as the Examiner suggests; there is no reasonable expectation of success were such modification to be undertaken; and most importantly, Dennis, La Fleur, Ide and/or Evans fail to teach Appellant's claimed invention even when combined as the Examiner proposes.³³

Appellant has not challenged the references' "combinability" or asserted that they are from different fields of endeavor, as the Examiner contends, but instead has persistently argued that one of skill in the art would not combine them and, even if s/he did, the limitations of the present claims still would not be met. Specifically, none of Dennis, La Fleur, Ide and/or Evans, alone or in combination, teaches the key claim element of degrading, by *in vitro* culturing, CSPG of a nerve graft. The Examiner has yet to fairly respond to this argument.

Conclusion

Appellant respectfully submits that the Examiner has failed to meet her burden of establishing that the limitations of the present claims are met by the references of record, alone

³¹ Answer at pg. 16.

³² Appeal Brief, pg. 19.

³³ Appellant's Appeal Brief, pgs. 20-21.

or in combination. Appellant therefore asks the Board of Patent Appeals and Interferences to reverse the Examiner's rejections and direct that this application be passed to issuance.

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Respectfully submitted,

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